37 C.F.R. § 41.202 requires a suggestion for interference to:

(1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference,

(2) Identify all claims the applicant believes interfere, propose one or more Counts, and show how the claims correspond to one or more Counts,

(3) For each Count, provide a claim chart comparing at least one claim of each party corresponding to the Count and show why the claims interfere within the meaning of § 41.203(a),

(4) Explain in detail why the applicant will prevail on priority,

(5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification, and

(6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter.

Applicants hereby notify the Examiner that the assignee of this application (AFFYMETRIX, INC.) has separately suggested an interference between U.S. Application No. 10/648,819 ("the '819 application") and the '196 and '820 patents.

II. 37 C.F.R. § 41.202(a)(1) - Identification of Patent

Applicants seek an interference with U.S. Patent Nos. 6,591,196 ("the '196 patent") and 6,768,820 ("the '820 patent"), issued to Yakhini *et al.* on July 8, 2003 and July 27, 2004, respectively.

III. 37 C.F.R. § 41.202(a)(2) – Identification of interfering claims, Proposed Count(s), and Claims Correspondence

A. Interfering Claims

37 C.F.R. § 41.203(a) provides as follows:

> An interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa.

Applicants' claim 28 corresponds exactly with the '196 patent claim 14. Applicants' claim 29 is similar to the '196 patent claim 15. Applicants' claim 30 corresponds exactly with the '820 patent claim 1. Likewise, Applicants' claim 31 corresponds exactly with the '820 patent claim 2. The claim chart below compares these claims as required under 37 C.F.R. § 41.202(a)(3). Therefore, at least these four claims are believed to "interfere" within the meaning of § 41.203(a).

Applicants' Claim	**'196 Patent Claim**
28. A system for automated extraction of data from a molecular array having features arranged in a regular pattern, the system comprising: a scanning component that produces images of the molecular array representing intensities of data signals emitted from discrete positions on a surface of the molecular array; a computer program that processes the images of the molecular array produced by the	14. A system for automated extraction of data from a molecular array having features arranged in a regular pattern, the system comprising: a scanning component that produces images of the molecular array representing intensities of data signals emitted from discrete positions on a surface of the molecular array; a computer program that processes the images of the molecular array produced by the

scanning component to index features in the images of the molecular array corresponding to molecules bound to features of the molecular array and that extracts data from the indexed features within images of the molecular array; and a computer for executing the computer program.	scanning component to index features in the images of the molecular array corresponding to molecules bound to features of the molecular array and that extracts data from the indexed features within images of the molecular array; and a computer for executing the computer program.
29. The system of claim 28 wherein data signal intensities emanating from discrete positions on the surface of the molecular array include: radiation emitted by radioisotopes incorporated into molecules bound to features of the molecular array; and fluorescent emission from fluorophores incorporated into molecules bound to features of the molecular array.	15. The system of claim 14 wherein data signal intensities emanating from discrete positions on the surface of the molecular array include: radiation emitted by radioisotopes incorporated into molecules bound to features of the molecular array; fluorescent emission from fluorophores incorporated into molecules bound to features of the molecular array; and light emission from chemoluminescent moieties incorporated into molecules bound to features of the molecular array.
Applicants' Claim	**'820 Patent Claim**
30. A method for evaluating an orientation of a molecular array having features arranged in a pattern, the method comprising:	1. A method for evaluating an orientation of a molecular array having features arranged in a pattern, the method comprising:

(a) receiving an image of the molecular array produced by scanning the molecular array to determine data signals emanating from discrete positions on a surface of the molecular array; (b) calculating an actual result of a function on pixels of the image lying in a second pattern; (c) comparing the result of step (b) with an expected result which would be obtained if the second pattern had a predetermined orientation on the array; and (d) when the results of the comparison in step (c) are outside a predetermined difference, then altering the orientation of the second pattern on the array and repeating steps (b) and (c), and repeating the foregoing as needed until the results of the comparison are within the predetermined difference.	(a) receiving an image of the molecular array produced by scanning the molecular array to determine data signals emanating from discrete positions on a surface of the molecular array; (b) calculating an actual result of a function on pixels of the image lying in a second pattern; (c) comparing the result of step (b) with an expected result which would be obtained if the second pattern had a predetermined orientation on the array; and (d) when the results of the comparison in step (c) are outside a predetermined difference, then altering the orientation of the second pattern on the array and repeating steps (b) and (c), and repeating the foregoing as needed until the results of the comparison are within the predetermined difference.

31. The method of claim 1 wherein: the features are arranged in a rectilinear grid and the pattern comprises a rectilinear grid of rows and columns; and step (b) comprises calculating row and column vectors by summing pixels in the rows and columns.	2. The method of claim 1 wherein: the features are arranged in a rectilinear grid and the pattern comprises a rectilinear grid of rows and columns; and step (b) comprises calculating row and column vectors by summing pixels in the rows and columns.

B. Proposed Count

For the purpose of the suggested interference, Applicants propose a single Count defined as follows:

Claim 14 of the '196 patent

or

Applicants' Claim 28

or

Claim 1 of the '820 patent

or

Applicants' Claim 30

As shown in § A, *supra*, claim 14 of the '196 patent corresponds exactly to Applicants' claim 28, and claim 1 of the '820 patent corresponds exactly to Applicants' claim 30.

C. Correspondence of Claims to Proposed Count

Under the provisions of 37 C.F.R.§ 41.207(b)(2), a claim corresponds to a Count if the subject matter of the Count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of the claim.

The claims of the parties that are believed to correspond to the proposed Count are as follows:

Applicants (Stern *et al.*):	Claims 28-31
Yakhini ('196 patent):	Claims 1-18
Yakhini ('820 patent):	Claims 1-5

Below, Applicants explain why the identified application claims should be designated as corresponding to the proposed Count.

1. Designation of Applicants' Claims 28-31

Applicants identify Applicants' claims 28-31 as corresponding to the proposed Count. Applicants' claim 28 is expressly recited in the definition of the proposed Count and, therefore, would be anticipated by the proposed Count. Applicants' claim 29, as amended in the concurrently filed Amendment, would have been obvious over the proposed Count in view of U.S. Patent No. 5,143,854 (" the '854 patent") because fluorescence and radiographic labeling techniques are discussed in the '854 patent. The '854 patent issued on September 1, 1992. Applicants' claim 30 is expressly recited in the definition of the proposed Count and, therefore, would be anticipated by the proposed Count. Applicants' claim 31 would have been obvious in view of the proposed Count and Shams' U.S. Patent No. 6,249,144 ("Shams' '144 patent") and Stern U.S. Patent No. 5,631,734 ("Stern's '734 patent"). Shams' '144 patent shows examples of features disposed in grids of rows and columns and also shows summing up the pixels in rows

and columns in mathematical formulae. Shams' '144 patent issued on February 19, 2002 and has an effective date of February 7, 1998. Stern's '734 patent provides at Col. 15, lines 61-66: "Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram or each cell at step 605." Stern's '734 patent issued on May 20, 1997 and has an effective date of February 10, 1994.

2. Designation of Yakhini '196 Claims 1-18

Below, Applicants explain why the identified patent claims should be designated as corresponding to the proposed Count.

Claims 1-18 of the `196 patent each would be anticipated or have been obvious over the proposed Count, treating the proposed Count as prior art to these claims, and, therefore, should be designated as corresponding to the proposed Count for at least the following reasons:

Claim 1. By way of claim 14 of the '196 patent, the proposed Count defines a system for automated extraction of data from a molecular array having features arranged in a regular pattern. The `196 claim 1 limitations would have been obvious over the proposed Count in view of Shams '144 patent, which has an effective date of February 7, 1998 under 35 U.S.C. § 102(e), which is prior to the earliest possible benefit date under 35 U.S.C. § 120 for the '196 patent of June 6, 2000. Shams' '144 patent shows a method for applying a grid to a molecular array. See the flow chart in Fig. 8 where images are received (step 64), a grid is generated with and estimate of initial positions (70) and a refined or adjusted position is generated (78). Fig. 3 has a similar disclosure with receiving and storing images (16), estimating/generating (26), adjusting/refining (28) and developing an initial coordinate system (26, 28, and 30). The Shams' '144 patent system uses "strong features" to locate and shift grid points, see Col. 6, lines 36 to

44. Multiple iterations of the process may be performed. Col. 6, lines 65-67. Low signal areas are also identified, see Col. 9, lines 52-59. Background values are acquired during this analysis, see Col. 4, line 49, Fig. 9 (step 90), Fig. 12 (Step 104), and others. Therefore, claim 1 of the '196 patent would have been obvious over the proposed Count in view of Shams' '144 patent and should be designated as corresponding thereto.

Claim 2. Claim 2 is dependent on claim 1 and claims different labels that are on the array, which are shown in Stern's '734 patent. "Fluorescent" is shown throughout the '734 patent (even in the title) and radiographic labels are shown in U.S. Patent No. 5,143,854 ("the '854 patent"), which was incorporated by reference at Col. 1. Chemiluminescent labels for arrays are shown in at least U.S. Patent No. 5,800,992 ("the '992 patent") and its foreign equivalent WO 92/10588. The '992 patent issued on September 1, 1998 and the PCT application was published on June 25, 1992. Therefore, claim 2 would have been obvious over the proposed Count in view of the '734, '854, and '992 patents and should therefore be designated as corresponding thereto.

Claim 3. Claim 3 is dependent on claim 1 and further specifies that the images are composed of pixels having intensity values, which features are shown in the Stern '734 patent in a multitude of locations, such as, Col. 8, line 58 to Col. 9, line 3. See also claim 2 of the Shams' '144 patent. Therefore, claim 3 would have been obvious over the proposed Count in view of the '734 and '144 patents and should therefore be designated as corresponding thereto.

Claim 4. Claim 4 is dependent on claim 3 and further recites arranging the array data into a grid using the corners and other information. Stern's '734 patent shows corner features as marker features (Col. 15, lines 60-61) and the use of rows and columns (as horizontal and vertical cells, see Col. 15, lines 62-63). Pixel intensities are shown in line 67. See also Col. 16, lines 20-26. The Shams' '144 patent shows the selection of an image region for grid

placement by defining the four corners for grid placement either by user selection or by anchor features (col. 6, line 7-14). The Shams' '144 patent also discloses employing row and column values in the computation of a direction vector (col. 7, line 17-55), and shifting each grid point towards regions with the highest intensity values, *i.e.* "peaks" (col. 6, lines 36-43). Therefore, claim 4 would have been obvious over the proposed Count in view of the '144 and '734 patents and should therefore be designated as corresponding thereto.

Claim 5. Claim 5 is dependent on claim 4 and claims calculating the rows and columns in various orientations, which is illustrated in the Shams' '144 patent at Col. 7, lines 17-55, which shows the calculation of direction vector. "An example calculation of the direction vector d for said bounding box size r X r is described below. The bounding box is represented as a matrix P in the memory 14 with n columns and m rows, and elements p_{ij} corresponding to image intensity values at a location (i,j) in the bounding box." Thus, the bounding box includes n columns and m rows where a direction vector is calculated for the bounding box. Also, at Col. 6, lines 36-43 of Shams' '144 patent: "Since it is assumed that the pixel intensity corresponding to DNA spots images 10 in the image region 18 are greater than their surrounding background 50 intensity values, the computer 34, according to the above steps, automatically shifts each grid point 24 towards local regions with the highest intensity values in subsequent iterations of said steps, wherein each grid point's location in the image frame 12 is modified". In addition, the Stern '734 patent provides an illustrative example of histograms based upon a measure of intensity that include peaks in Fig. 6A, where the histograms are analyzed to identify the distinct peaks (steps 606 and 607, and col. 16, lines 1-19). Therefore, claim 5 would have been obvious over the proposed Count in view of the '144 and '734 patents and should therefore be designated as corresponding thereto.

Claim 6. Claim 6 is dependent on claim 3 and would have been obvious over the proposed Count in view of the Shams '144 patent at Col. 7, line 17-55, which illustrates the calculation of direction vector. See the '196 Patent definition of Blob analysis at Col. 10 lines 43-53 in which it is stated: "Blob analysis comprises the analysis of pixels within a region of interest encompassing the estimated position of a feature in order to first determine a threshold pixel intensity value and to then create a binary image in which all pixels having pixel intensity values greater than the threshold value are assigned the value '1,' and all pixels having pixel intensity values in the region of interest less than the threshold value are assigned the value '0' The coordinates of the centroid of the connected collection of pixels closest to the center of the region of interest in the binary image is then taken to be the refined pixel coordinates corresponding to the center of the feature." The term "Binary" usually means consisting of two parts or two separate elements. Thus, for each grid point (analogous to selected marker feature) Shams' 144 patent discloses the combination of direction vectors d and e (two separate elements) to refine the position of the grid point. At Col. 8, lines 49-51, Shams' '144 patent provides: "The computer 34 then linearly combines the direction vectors d and e to obtain a direction vector t for updating the position of the grid point 24." As illustrated in Figure 7, the grid point is substantially at the center of the feature. Therefore, claim 6 would have been obvious over the proposed Count in view of the '144 patent and should therefore be designated as corresponding thereto.

Claim 7. Claim 7 is dependent on claim 6 and generally claims selecting different intensity bands for the pixels. Claim 7 would have been obvious over the proposed Count in view of Fodor *et al.* U.S. Patent No. 6, 124,102 ("the '102 patent", filed on April 21, 1998 and issued on September 26, 2000), and standard statistical techniques. See, for example, claims 1

and 16 of Fodor's '102 patent. See also Stern's '734 patent at Fig. 6A.

Claim 8. Claim 8 is dependent on claim 6 and also generally claims selecting different intensity bands for the pixels. Claim 8 would have been obvious over the proposed Count in view Fodor's '102 patent and standard statistical techniques. See, for example, claims 1 and 16 of Fodor's '102 patent and Stern's '734 patent at Fig. 6A.

Claim 9. Claim 9 is dependent on claim 3, generally claims setting a size band for a blob, and would have been obvious over the proposed Count in view of the prior art cited for claim 6 (Shams' '144 patent and Stern's `734 patent) and standard statistical techniques.

Claim 10. Claim 10 is dependent on claim 9 and would have been obvious over the proposed Count in view of Shams' '144 patent at Col. 11, lines 41-58, which discloses displaying a plurality of DNA spot images, analyzing the background and signal intensity values and for each DNA spot relating the analyzed difference values.

Claim 11. Claim 11 is dependent on claim 3 and generally claims using linear regression analysis to produce refined features. This technique is a standard analytical tool and Claim 11 would have been obvious over the proposed Count in view of the prior art cited for claim 3 plus any standard reference for this technique.

Claim 12. Claim 12 is dependent on claim 11, recites standard statistical methods as applied to the array analysis, and would have been obvious over the proposed Count in view of Shams' '144 patent and Stern's `734 patent, the art cited during prosecution and standard texts on the subject of statistical analysis.

Claim 13. Claim 13 is dependent on claim 1, recites standard statistical methods as applied to the array analysis, and would have been obvious over the proposed Count in view of Shams' '144 patent and Stern's `734 patent, the art cited during prosecution and standard texts

on the subject of statistical analysis.

Claim 14. Claim 14 is specifically recited in the Count and therefore the Count would anticipate claim 14.

Claim 15. Claim 15 is subject to the same analysis as claim 2 above

Claim 16. Claim 16 is subject to the same analysis as claim 1 above.

Claim 17. Claim 17 is dependent on claim 16 and recites multiple statistical methods to apply to features in the array. This claim would have been obvious over the proposed Count in view of Shams' '144 patent and Stern's '734 patent, the art cited during prosecution and standard texts on the subject of statistical analysis.

Claim 18. Claim 18 is dependent on claim 16 and recites multiple statistical methods to apply to features in the array. This claim would have been obvious over the proposed Count in view of Shams' '144 patent and Stern's '734 patent, the art cited during prosecution and standard texts on the subject of statistical analysis.

3. *Designation of Yakhini '820 Claims 1-5*

Below, Applicants explain why the identified patent claims should be designated as corresponding to the proposed Count.

Claims 1-5 of the '820 patent would be anticipated or have been obvious in view of the proposed Count, treating the proposed Count as prior art to these claims, and, therefore, should be designated as corresponding to the proposed Count for the following reasons:

Claim 1. Claim 1 is specifically recited in the Count and therefore defines the same patentable invention as the Count.

Claim 2. Claim 2 is dependent on claim 1 and limits the arrangement of the features to a grid and a method for calculating vectors. Stern's '734 patent shows corner features as

marker features (Col. 15, lines 60-61) and the use of rows and columns (as horizontal and vertical cells, see Col. 15, lines 62-63). Pixel intensities are shown in line 67. See also Col. 16, lines 20-26. Shams' '144 patent shows examples of features disposed in grids of rows and columns in Figs. 1, 2, 4-7 and col. 5, lines 28-47 of the specification. Shams' '144 patent shows summing up pixels in rows and columns in the mathematical formulae presented in col. 7, lines 23-55, where there are pixel intensity values associated with n columns and m rows used in various computations to compute an average or weighted sum of vectors described in col. 7, lines 2-16. Therefore, claim 2 would have been obvious over the proposed Count in view of the '144 and '734 patents and should therefore be designated as corresponding thereto.

Claim 3. Claim 3 is dependent on claim 1 and is limited to associating a code with an array and would have been obvious over the proposed Count in view of Shams' '144 patent and others. For example, the code may be a bar code (see Yakhini's `820 patent at col. 27, line 44). Bar codes for arrays are claimed in U.S. Patent No. 6,399,365, which has a priority date of June 8, 1994. This disclosure was issued earlier as U.S. Patent No. 5,945,334 on August 31, 1999 and its foreign equivalent was published on February 7, 1996 as EP 695 941. Therefore, claim 3 would have been obvious over the proposed Count in view of the patents discussed herein and should therefore be designated as corresponding thereto.

Claim 4. Claim 4 is dependent on Claim 3 and is limited to obtaining information from a remote location. Claim 4 would have been obvious over the proposed Count in view of Shams' '144 patent. Layout information is obtained after synthesis and a special file is sent to the customer with the commercial array. Synthesis occurs at the manufacturing facility which is in another building from where a customer would use the array. Therefore, claim 4 would have been obvious over the proposed Count in view of the '144 patent and should therefore be

designated as corresponding thereto.

Claim 5. Claim 5 is dependent on claim 1 and specifies rotational orientation. United States Patent No. 6,090,555 to Fiekowsky *et al.* ("Fiekowsky's '555 patent"), which issued on July 18, 2000 and has a effective date of December 11, 1997, discloses at Col. 2, lines 17-18 the analysis of data to include "the steps of determining intensity as a function of substrate position," where the function of substrate position is analogous to an orientation of the data signals associated with positions on the substrate. Further, Fiekowsky's '555 patent illustrates that a rotational orientation is inherently included in the range of possible orientations of 2 dimensional probe array positioned in a perpendicular plane to an incident light beam (see Figures 1A-1C of Fiekowsky's '555 patent with respect to substrate 230). Therefore, claim 5 would have been obvious over the proposed Count in view of the '555 patent and should therefore be designated as corresponding thereto.

IV. <u>37 C.F.R. §§ 41.202 (a)(4) and 41.202(d) – Applicant will prevail on priority</u>

Applicants' present application claims benefit through a series of continuation applications to an application filed on February 10, 1994, *i.e.*, U.S. Patent Application No. 08/195,889 ("the '889 application"). The chart set forth in § VI, below, shows that the '889 application provides a constructive reduction to practice within the scope of the interfering subject matter.

In comparison, the earliest <u>possible</u> constructive reduction to practice to which the '196 and '820 patents may be accorded benefit is an application (09/589,046) filed on June 6, 2000.

Therefore, Applicants will *prima facie* prevail on priority based on a constructive reduction to practice that precedes (by <u>six years and four months</u>) the earliest <u>possible</u> constructive reduction to practice that may be accorded to the '196 and '820 patents.

V. 37 C.F.R. §§ 41.202(a)(5) – Written Description for each claim in the Applicant's specification

Applicants have added claims 28-31 to provoke the suggested interference. In accordance with 37 C.F.R. § 41.202(a)(5), Applicants provide a claim chart showing the written description in the Applicants' specification for each of the added claims.

Claims Added	Disclosure in Applicants' Specification
28. A system for automated extraction of data from a molecular array having features arranged in a regular pattern, the system comprising:	"The invention provides a method and associated apparatus for detecting and analyzing reactions of fluorescently marked materials on a single substrate surface." p. 1, lines 9-11; "Methods and devices for the detection of fluorescently labeled targets on a substrate are disclosed. The detection method and devices utilize a substrate having a large variety of probes at known locations on its surface." p. 2, lines 21-24; ""The confocal detection device includes a monochromatic or polychromatic light source, means for directing an excitation light from the light source at the substrate, means for focusing the light on the substrate, means for controlling temperature of the substrate during a reaction, means for detecting fluorescence emitted by the targets in response to the excitation light by directing the fluorescence through confocal pinholes, and means for identifying the region where the fluorescence originated. The means for controlling the temperature may include a temperature controlled fluid filled flow cell. The means for detecting the fluorescent emissions from the substrate, in some embodiments, include a photomultiplier tube. The means for focusing the excitation light to a point on the substrate and determining the region the fluorescence originated from may include an x-y-z translation table. Further, translation of the x-y-z table, temperature control and data collection are recorded and managed by an appropriately programmed digital computer. In connection with one aspect of the invention, methods for analyzing the data collected by the fluorescent detection methods and devices are disclosed. Data analysis includes the steps of determining fluorescent intensity as a function of substrate position from the data collected; removing "outliers" (data deviating from a predetermined statistical distribution); and calculating the relative binding affinity of the targets from the remaining data. The resulting data are displayed as an image with the intensity in each region varying according to the binding affinity between targets and probes therein." p. 2, line 28 to p. 3, line 19; "Referring to Fig. 6, the system is initialized by requesting the

	user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 22-32; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.
a scanning component that produces images of the molecular array representing intensities of data signals emitted from discrete positions on a surface of the molecular array;	"A photon counter detects fluorescence from the substrate, while an x-y translation stage varies the location of the substrate." p.1, lines 21-23; "The confocal detection device includes a monochromatic or polychromatic light source, means for directing an excitation light from the light source at the substrate, means for focusing the light on the substrate, means for controlling temperature of the substrate during a reaction, means for detecting fluorescence emitted by the targets in response to the excitation light by directing the fluorescence through confocal pinholes, and means for identifying the region where the fluorescence originated." p.2, lines 28-36; "The means for detecting the fluorescent emissions from the substrate, in some embodiments, include a photomultiplier tube. The means for focusing the excitation light to a point on the substrate and determining the region the fluorescence originated from may include an x-y-z translation table." p. 2, line 38 to p. 3, line 5; "In connection with one aspect of the invention, methods for analyzing the data collected by the fluorescent detection methods and devices are disclosed. Data analysis includes the steps of determining fluorescent intensity as a function of substrate position from the data collected; removing "outliers" (data deviating from a predetermined statistical distribution); and calculating the relative binding affinity of the targets from the remaining data. The resulting data are displayed as an image with the intensity in each region varying according to the binding affinity between targets and probes therein." p. 3, lines 9-19; "Fig. 1a schematically illustrates a device used to detect fluorescently labeled targets on a substrate." p. 6, lines 10-11; "Flow cell 220 is mounted on a x-y-z translation table 230. X

	represents the horizontal direction; y represents the vertical direction; and z represents the direction into and away from the microscope objective such that focusing may be performed. In some embodiments, the x-y-z translation table may be a Pacific Precision Laboratories Model ST-SL06R-B5M." p. 8, lines 4-9; "After data are collected from a region of the substrate, substrate 230 is moved so that light can be directed at a different region on the substrate. The process is repeated until all regions on the substrate have been scanned. Generally, regions that contain a complementary probe will tend to exhibit a higher photon count than regions that do not contain a complementary probe." p. 12, lines 21-27; "The TTL pulses, each one corresponding to a photon detected by the photomultiplier tube, are then collected by a data acquisition board 210. The data acquisition board may be a National Instruments "Lab-PC+" or equivalent. Data acquisition board 210, typically, contains an Intel 8254 or equivalent counter/timer chip. This chip contains three counters, counter 0, counter 1 and counter 2. Counter 0 controls the operations of counters 1 and 2 for collecting data. Preferably, counter 0 is programmed to generate a square wave with a period which is equal to twice the data acquisition time per pixel. The output of counter 0 is coupled to an external circuit board 200 which provides logic for inverting the square wave. In a preferred embodiment, the inverted output of counter 0 is connected to the gate input of counter 2 while the non-inverted output is connected to the gate input of counter 1." p. 11, lines 20-36; "The number of scan parameter corresponds to the number of times the user wishes to scan the substrate while the time between scans parameter controls the amount of time to wait before commencing a subsequent scan. In this manner, the user may perform a series of scan and if desired, each at a different temperature. Preferably, the time between scans is chosen to allow the system to reach chemical equilibrium before commencing a subsequent scan." p. 17, line 10-17; "At step 202, the system initializes the x-y-z translation table by locating the x-y-z stages at their home position. At step 203, the system focuses the laser on the surface 231 of the substrate. At step 204, the system locates the x-y-z table at its start position. At step 205, the system begins to translate the vertical stage, thereby collecting a series of data points over a vertical line at step 206. When a line of pixels has been scanned at step 207, the x-y-z translation table moves the horizontal stage to collect data from the next line of pixels at step 208. The collected data is written to the file as the substrate is repositioned at the top of the

	next line. Steps 205 through 208 are repeated until data from all regions have been collected. At step 209, the system determines if there are any more scans to be performed according to the set up parameters. If there are, the system at steps 210 and 211 determines the amount of time to wait before commencing the next scan and to either repeat the process from step 203 (if refocusing of the substrate is desired) or 204. Otherwise, the scan is terminated." p. 17, line 36 to p. 18, line 17; "Fig. 4a illustrates the data acquisition process beginning at step 205 in greater detail. In a specific embodiment, data are collected by repeatedly scanning the substrate in vertical lines until the sample is completely scanned However, other techniques such as repeatedly scanning the substrate in horizontal lines, bidirectional scanning (acquiring data in both directions) or others may be employed." p. 20, lines 21-28; "Upon completion, the system creates a data file wherein the data represents an array of photon counts as a function of substrate position. By counting the number of photons generated in a given area in response to the excitation light, it is possible to determine where fluorescently marked molecules are located on the substrate. Consequently, it is possible to determine which of the probes within a matrix of probes is complementary to a flourescently marked target." p. 23, lines 8-17; Figs. 1A-C show scanners. Figs 2, 3A, 3B, 4A, 4B, 4C and 5 show the system for generating, receiving and analyzing data from an array.
a computer program that processes the images of the molecular array produced by the scanning component to index features in the images of the molecular array corresponding to molecules bound to features of the molecular array and that extracts data from the indexed features within images of the molecular array;	"Upon completion of the conversion process, an image file representing fluorescence intensity is created and stored in memory at step 507. At step 508, the system may optionally display the image file. The intensity level of the displayed image varies from region to region according to the binding affinity of the targets to the polymer sequence therein. The brightest signals typically represent the greatest binding affinity while signals of lesser intensity represent lesser degrees of binding affinity." p. 25, lines 29-37; "Fig. 6 illustrates one embodiment of the of a system which provides for the removal of these undesirable spurious data points as well as the determination of the relative binding efficiency of the sample from an average of the remaining data points. Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the

	information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 17-32; "Further, the user, at step 614, may analyze a specific synthesis region within the grid. If instructed, the system will display the corresponding substrate position, number of photons, number of pixels and the molecular sequence at that synthesis site. The data analysis software also provides the user with many functions which are common to image processing, such as magnification and image enhancement." p. 28, lines 1-7; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.
and a computer for executing the computer program.	"A computer controls the movement of the x-y translation table and data collection. Such devices are discussed in, for example, U.S. Pat No. 5,143,854 (Pirrung *et al.*) incorporated herein by reference for all purposes. See also PCT WO 92/10092 also incorporated herein by reference for all purposes." p. 1, lines 23-29; "Further, translation of the x-y-z table, temperature control and data collection are recorded and managed by an appropriately programmed digital computer." p. 3, lines 5-8; "Photodiode may be, for example, a 13 DSI007 made by Melles Griot or equivalent, or other light detection devices, such as photomultiplier tube or avalanche photodiode may be used. Output from the detection device is used by computer 190 to focus the laser at a point on surface 231 of substrate 230." p. 10, lines 26-31; "The output of the C3866 preamplifier/discriminator, via external circuit board 200, is connected to the clock inputs of counters 1 and 2. When counter 1 or counter 2 is gated on, it counts pulses generated by the preamplifier/discriminator; when it is gated off, it ceases to count and computer 190 reads the accumulated number of counts therein. After the computer reads the count from either counter 1 or 2, the counter is re-initialized on the first clock pulse after its gate input goes high. The initialization pulse is about a 50 ns pulse that is generated by the logic in the external circuit board 200 about 50 ns after each transition of the square wave signal from counter 0. The data stored in counter 1 or 2 represents the photon count as a function of substrate position." p. 12, lines 7-20; "The computer reads and stores the voltage generated by the

	photodiode at step 308." p. 19, lines 19-21; "On the second pass of the loop beginning at step 405, the inverted falling edge (rising edge) of the square wave initializes and enables counter 1 to collect data at steps 406 and 407 respectively. At step 408, the inverted rising edge (falling edge) of the square wave disables counter 1 and data therein is read at step 409 and written to the computer at step 410." p. 22, lines 7-13; "From the information entered by the user and the image file, the system creates a computer representation of a histogram or each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 28-32; "Upon completion of the conversion process, an image file representing fluorescence intensity is created and stored in memory at step 507." p. 25, lines 29-31.
29. (As Amended) The system of claim 28 wherein data signal intensities emanating from discrete positions on the surface of the molecular array include:	<u>System:</u> "The invention provides a method and associated apparatus for detecting and analyzing reactions of fluorescently marked materials on a single substrate surface." p. 1, lines 9-11; "Methods and devices for the detection of fluorescently labeled targets on a substrate are disclosed. The detection method and devices utilize a substrate having a large variety of probes at known locations on its surface." p. 2, lines 21-24; "The confocal detection device includes a monochromatic or polychromatic light source, means for directing an excitation light from the light source at the substrate, means for focusing the light on the substrate, means for controlling temperature of the substrate during a reaction, means for detecting fluorescence emitted by the targets in response to the excitation light by directing the fluorescence through confocal pinholes, and means for identifying the region where the fluorescence originated. The means for controlling the temperature may include a temperature controlled fluid filled flow cell. The means for detecting the fluorescent emissions from the substrate, in some embodiments, include a photomultiplier tube. The means for focusing the excitation light to a point on the substrate and determining the region the fluorescence originated from may include an x-y-z translation table. Further, translation of the x-y-z table, temperature control and data collection are recorded and managed by an appropriately programmed digital computer. In connection with one aspect of the invention, methods for analyzing the data collected by the fluorescent detection methods and devices are disclosed. Data analysis includes the steps of determining fluorescent intensity as a function of substrate position from the data collected; removing "outliers"

	(data deviating from a predetermined statistical distribution); and calculating the relative binding affinity of the targets from the remaining data. The resulting data are displayed as an image with the intensity in each region varying according to the binding affinity between targets and probes therein." p. 2, line 28 to p. 3, line 19; "Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 22-32; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image. <u>Data signal intensities:</u> "According to preferred embodiments, the intensity and duration of the light applied to the substrate is controlled by the computer according to the set up parameters entered at step 201. By varying the laser power and scan stage rate, the signal-to-noise ratio may be improved by maximizing fluorescence emissions. As a result, the present invention can detect the presence or absence of a target on a probe as well as determine the relative binding affinity of targets to a variety of sequences." p. 23, lines 18-26; "Before the data file representing an array of photon counts as a function of position is analyzed to determine the relative binding affinity of targets, the data file is preferably converted to an image file wherein the data is indicative of fluorescence intensity level as a function of substrate position. Fig. 5 illustrates the process for converting or scaling the data from photon counts to fluorescence intensity level in greater detail. The conversion procedure is started by prompting the operator for the name of data file of interest. At step 501, the system retrieves the specified data file for analysis." p. 24, lines 15-26; "Upon completion of the conversion process, an image file representing fluorescence intensity is created and stored in memory at step 507. At step 508, the system may optionally

	display the image file. The intensity level of the displayed image varies from region to region according to the binding affinity of the targets to the polymer sequence therein. The brightest signals typically represent the greatest binding affinity while signals of lesser intensity represent lesser degrees of binding affinity." p. 25, lines 29-37; "A plot of the number of pixels versus the fluorescence intensity for a scan of a substrate synthesized with probes when it has been exposed to, for example, a labeled antibody will typically take the form of a bell curve. However, spurious data are observed, particularly at higher intensities. Since it is preferable to used an average of the fluorescence intensity over a given synthesis region in determining the relative binding affinity, these spurious data points will tend to undesirably skew the data." p. 26, lines 8-16; Fig. 5 which is a flow chart illustrating the method of converting data representing photon counts as a function of position to data representing fluorescence intensity level as a function of position.
radiation emitted by radioisotopes incorporated into molecules bound to features of the molecular array; and	"The resulting substrate will have a variety of uses including, for example, screening large numbers of polymers for biological activity. To screen for biological activity, the substrate is exposed to one or more receptors such as antibodies, whole cells, receptors on vesicles, lipids, or any one of a variety of other receptors. The receptors are preferably labeled with, for example, a fluorescent marker, radioactive marker, or a labeled antibody reactive with the receptor. The location of the marker on the substrate is detected with, for example, photon detection or autoradiographic techniques. Through knowledge of the sequence of the material at the location where binding is detected, it is possible to quickly determine which sequence binds with the receptor and, therefore, the technique can be used to screen large numbers of peptides." Col. 3, lines 39-54 of U.S. Patent No. 5,143,854, which was incorporated by reference at pages 1 and 6 of the specification at the time of filing and which has been requested to be added after the third full paragraph on page 2 by an Amendment filed concurrently herewith.
fluorescent emission from fluorophores incorporated into molecules bound to features of the molecular array.	"The invention provides a method and associated apparatus for detecting and analyzing reactions of fluorescently marked materials on a single substrate surface." p. 1, lines 9-11; "Methods and devices for the detection of fluorescently labeled targets on a substrate are disclosed. The detection method and devices utilize a substrate having a large variety of probes at known locations on its surface. The substrate, when placed in a confocal detection device, is exposed to fluorescently labeled targets that bind to one of more of the probes. The confocal detection device includes a monochromatic

	or polychromatic light source, means for directing an excitation light from the light source at the substrate, means for focusing the light on the substrate, means for controlling temperature of the substrate during a reaction, means for detecting fluorescence emitted by the targets in response to the excitation light by directing the fluorescence through confocal pinholes, and means for identifying the region where the fluorescence originated." p. 2, lines 21-36; "The means for controlling the temperature may include a temperature controlled fluid filled flow cell. The means for detecting the fluorescent emissions from the substrate, in some embodiments, include a photomultiplier tube." p. 2, line 37 to p. 3, line 2; "Data analysis includes the steps of determining fluorescent intensity as a function of substrate position from the data collected." p. 3, lines 11-13; "Strong binding affinity will be evidenced herein by a strong fluorescence signal since many target molecules will bind to that probe." p. 23, lines 29-31. "The resulting substrate will have a variety of uses including, for example, screening large numbers of polymers for biological activity. To screen for biological activity, the substrate is exposed to one or more receptors such as antibodies, whole cells, receptors on vesicles, lipids, or any one of a variety of other receptors. The receptors are preferably labeled with, for example, a fluorescent marker, radioactive marker, or a labeled antibody reactive with the receptor. The location of the marker on the substrate is detected with, for example, photon detection or autoradiographic techniques. Through knowledge of the sequence of the material at the location where binding is detected, it is possible to quickly determine which sequence binds with the receptor and, therefore, the technique can be used to screen large numbers of peptides." Col. 3, lines 39-54 of U.S. Patent No. 5,143,854, which was incorporated by reference at pages 1 and 6 of the specification at the time of filing and which has been requested to be added after the third full paragraph on page 2 by an Amendment filed concurrently herewith.
30. A method for evaluating an orientation of a molecular array having features arranged in a pattern, the method comprising:	"Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file)

	plots the number of pixels versus intensity." p. 26, lines 22-32; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.
(a) receiving an image of the molecular array produced by scanning the molecular array to determine data signals emanating from discrete positions on a surface of the molecular array;	"Upon completion of the conversion process, an image file representing fluorescence intensity is created and stored in memory at step 507. At step 508, the system may optionally display the image file. The intensity level of the displayed image varies from region to region according to the binding affinity of the targets to the polymer sequence therein. The brightest signals typically represent the greatest binding affinity while signals of lesser intensity represent lesser degrees of binding affinity." p. 25, lines 29-37 "Fig. 6 illustrates one embodiment of the of a system which provides for the removal of these undesirable spurious data points as well as the determination of the relative binding efficiency of the sample from an average of the remaining data points. Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity. At step 606, the main data analysis loop is performed for each synthesis site. Analyzing the histogram for the respective synthesis site, the system calculates the total intensity level and number of pixels for the bandwidth centered around varying intensity levels. For example, as shown in the plots to the right of step 606, the system calculates the number of pixels in the bandwidth using boxcar averaging technique. This process is then repeated until the entire range of intensities have been scanned. At step 607, the system determines which band has the highest total number of pixels. The data form this band is used to derive statistical data for each synthesis site. The statistical data include the peak value, mean intensity and standard deviation of intensity level. Thus, data that are beyond this band are excluded from the statistical analysis. Assuming the bandwidth is selected to be reasonably small, this procedure will have the effect of eliminating spurious data located at both the higher and lower

	intensity levels. This loop is repeated until all the cells have been processed." p. 26, line 22-p. 27, line 13; Figs. 1A-C show scanners. Figs 2, 3A, 3B, 4A, 4B, 4C and 5 show the system for generating, receiving and analyzing data from an array.
(b) calculating an actual result of a function on pixels of the image lying in a second pattern;	"At step 610, an image in the form of a grid representing the substrate is displayed. Each block in the grid represents a region synthesized with a polymer sequence. The image intensity of each region will vary according to the binding affinity between the polymer sequence and targets therein. Statistical data, such as the peak and average intensity corresponding to each region are also displayed." p. 27, lines 14-20.
(c) comparing the result of step (b) with an expected result which would be obtained if the second pattern had a predetermined orientation on the array; and	"At step 612, the system retrieves the file created during the synthesis process of the substrate being analyzed. The synthesis file contains sequence information as a function of location. The system integrates the synthesis file with the image file and sorts the data therein. Through this process, the molecular sequence of complementary probes and the intensity as a function of location is available." p. 27, lines 31-37.
(d) when the results of the comparison in step (c) are outside a predetermined difference, then altering the orientation of the second pattern on the array and repeating steps (b) and (c), and repeating the foregoing as needed until the results of the comparison are within the predetermined difference.	"Fig. 6 illustrates one embodiment of the of a system which provides for the removal of these undesirable spurious data points as well as the determination of the relative binding efficiency of the sample from an average of the remaining data points. Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 17-32; "Further, the user, at step 614, may analyze a specific synthesis region within the grid. If instructed, the system will display the corresponding substrate position, number of photons, number of pixels and the molecular sequence at that synthesis site. The data analysis software also provides the user with many functions which are common to image processing, such as magnification and image enhancement." p. 28, lines 1-7; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.

31. The method of claim 1 wherein: the features are arranged in a rectilinear grid and the pattern comprises a rectilinear grid of rows and columns; and	"Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 22 – 32; "At step 610, an image in the form of a grid representing the substrate is displayed. Each block in the grid represents a region synthesized with a polymer sequence. The image intensity of each region will vary according to the binding affinity between the polymer sequence and targets therein. Statistical data, such as the peak and average intensity corresponding to each region are also displayed." p. 27, lines 14-20; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.
step (b) comprises calculating row and column vectors by summing pixels in the rows and columns.	"At step 606, the main data analysis loop is performed for each synthesis site. Analyzing the histogram for the respective synthesis site, the system calculates the total intensity level and number of pixels for the bandwidth centered around varying intensity levels. For example, as shown in the plots to the right of step 606, the system calculates the number of pixels in the bandwidth using boxcar averaging technique. This process is then repeated until the entire range of intensities have been scanned. At step 607, the system determines which band has the highest total number of pixels. The data from this band is used to derive statistical data for each synthesis site. The statistical data include the peak value, mean intensity and standard deviation of intensity level." p. 26, line 33 – p. 27, line 8; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.

VI. 37 C.F.R. § 41.202(a)(6) – Applicants' Earliest Constructive Reduction to Practice

For the purpose of the suggested interference, Applicants are entitled to the benefit of 08/195,889, filed February 10, 1994, which constitutes a constructive reduction to practice of an embodiment within the scope of the interfering subject matter, as reflected in the table below.

Claim 28 (recited in proposed Count)	Specification of 08/195,889
28. A system for automated extraction of data from a molecular array having features arranged in a regular pattern, the system comprising:	"The invention provides a method and associated apparatus for detecting and analyzing reactions of fluorescently marked materials on a single substrate surface." p. 1, lines 9-11; "Methods and devices for the detection of fluorescently labeled targets on a substrate are disclosed. The detection method and devices utilize a substrate having a large variety of probes at known locations on its surface." p. 2, lines 21-24; "The confocal detection device includes a monochromatic or polychromatic light source, means for directing an excitation light from the light source at the substrate, means for focusing the light on the substrate, means for controlling temperature of the substrate during a reaction, means for detecting fluorescence emitted by the targets in response to the excitation light by directing the fluorescence through confocal pinholes, and means for identifying the region where the fluorescence originated. The means for controlling the temperature may include a temperature controlled fluid filled flow cell. The means for detecting the fluorescent emissions from the substrate, in some embodiments, include a photomultiplier tube. The means for focusing the excitation light to a point on the substrate and determining the region the fluorescence originated from may include an x-y-z translation table. Further, translation of the x-y-z table, temperature control and data collection are recorded and managed by an appropriately programmed digital computer. In connection with one aspect of the invention, methods for analyzing the data collected by the fluorescent detection methods and devices are disclosed. Data analysis includes the steps of determining fluorescent intensity as a function of substrate position from the data collected; removing "outliers" (data deviating from a predetermined statistical distribution); and calculating the relative binding affinity of the targets from the remaining data. The

	resulting data are displayed as an image with the intensity in each region varying according to the binding affinity between targets and probes therein." p. 2, line 28 to p. 3, line 19; "Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 22-32; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.
a scanning component that produces images of the molecular array representing intensities of data signals emitted from discrete positions on a surface of the molecular array;	"A photon counter detects fluorescence from the substrate, while an x-y translation stage varies the location of the substrate." p.1, lines 21-23; "The confocal detection device includes a monochromatic or polychromatic light source, means for directing an excitation light from the light source at the substrate, means for focusing the light on the substrate, means for controlling temperature of the substrate during a reaction, means for detecting fluorescence emitted by the targets in response to the excitation light by directing the fluorescence through confocal pinholes, and means for identifying the region where the fluorescence originated." p.2, lines 28-36; "The means for detecting the fluorescent emissions from the substrate, in some embodiments, include a photomultiplier tube. The means for focusing the excitation light to a point on the substrate and determining the region the fluorescence originated from may include an x-y-z translation table." p. 2, line 38 to p. 3, line 5; "In connection with one aspect of the invention, methods for analyzing the data collected by the fluorescent detection methods and devices are disclosed. Data analysis includes the steps of determining fluorescent intensity as a function of substrate position from the data collected; removing "outliers" (data deviating from a predetermined statistical distribution); and calculating the relative binding affinity of

	the targets from the remaining data. The resulting data are displayed as an image with the intensity in each region varying according to the binding affinity between targets and probes therein." p. 3, lines 9-19; "Fig. 1a schematically illustrates a device used to detect fluorescently labeled targets on a substrate." p. 6, lines 10-11; "Flow cell 220 is mounted on a x-y-z translation table 230. X represents the horizontal direction; y represents the vertical direction; and z represents the direction into and away from the microscope objective such that focusing may be performed. In some embodiments, the x-y-z translation table may be a Pacific Precision Laboratories Model ST-SL06R-B5M." p. 8, lines 4-9; "After data are collected from a region of the substrate, substrate 230 is moved so that light can be directed at a different region on the substrate. The process is repeated until all regions on the substrate have been scanned. Generally, regions that contain a complementary probe will tend to exhibit a higher photon count than regions that do not contain a complementary probe." p. 12, lines 21-27; "The TTL pulses, each one corresponding to a photon detected by the photomultiplier tube, are then collected by a data acquisition board 210. The data acquisition board may be a National Instruments "Lab-PC+" or equivalent. Data acquisition board 210, typically, contains an Intel 8254 or equivalent counter/timer chip. This chip contains three counters, counter 0, counter 1 and counter 2. Counter 0 controls the operations of counters 1 and 2 for collecting data. Preferably, counter 0 is programmed to generate a square wave with a period which is equal to twice the data acquisition time per pixel. The output of counter 0 is coupled to an external circuit board 200 which provides logic for inverting the square wave. In a preferred embodiment, the inverted output of counter 0 is connected to the gate input of counter 2 while the non-inverted output is connected to the gate input of counter 1." p. 11, lines 20-36; "The number of scan parameter corresponds to the number of times the user wishes to scan the substrate while the time between scans parameter controls the amount of time to wait before commencing a subsequent scan. In this manner, the user may perform a series of scan and if desired, each at a different temperature. Preferably, the time between scans is chosen to allow the system to reach chemical equilibrium before commencing a subsequent scan." p. 17, line 10-17;

	"At step 202, the system initializes the x-y-z translation table by locating the x-y-z stages at their home position. At step 203, the system focuses the laser on the surface 231 of the substrate. At step 204, the system locates the x-y-z table at its start position. At step 205, the system begins to translate the vertical stage, thereby collecting a series of data points over a vertical line at step 206. When a line of pixels has been scanned at step 207, the x-y-z translation table moves the horizontal stage to collect data from the next line of pixels at step 208. The collected data is written to the file as the substrate is repositioned at the top of the next line. Steps 205 through 208 are repeated until data from all regions have been collected. At step 209, the system determines if there are any more scans to be performed according to the set up parameters. If there are, the system at steps 210 and 211 determines the amount of time to wait before commencing the next scan and to either repeat the process from step 203 (if refocusing of the substrate is desired) or 204. Otherwise, the scan is terminated." p. 17, line 36 to p. 18, line 17; "Fig. 4a illustrates the data acquisition process beginning at step 205 in greater detail. In a specific embodiment, data are collected by repeatedly scanning the substrate in vertical lines until the sample is completely scanned However, other techniques such as repeatedly scanning the substrate in horizontal lines, bidirectional scanning (acquiring data in both directions) or others may be employed." p. 20, lines 21-28; "Upon completion, the system creates a data file wherein the data represents an array of photon counts as a function of substrate position. By counting the number of photons generated in a given area in response to the excitation light, it is possible to determine where fluorescently marked molecules are located on the substrate. Consequently, it is possible to determine which of the probes within a matrix of probes is complementary to a flourescently marked target." p. 23, lines 8-17; Figs. 1A-C show scanners. Figs 2, 3A, 3B, 4A, 4B, 4C and 5 show the system for generating, receiving and analyzing data from an array.
a computer program that processes the images of the molecular array produced by the scanning component to index features in the images of the	"Upon completion of the conversion process, an image file representing fluorescence intensity is created and stored in memory at step 507. At step 508, the system may optionally display the image file. The intensity level of the displayed image varies from region to region according to

molecular array corresponding to molecules bound to features of the molecular array and that extracts data from the indexed features within images of the molecular array;	the binding affinity of the targets to the polymer sequence therein. The brightest signals typically represent the greatest binding affinity while signals of lesser intensity represent lesser degrees of binding affinity." p. 25, lines 29-37; "Fig. 6 illustrates one embodiment of the of a system which provides for the removal of these undesirable spurious data points as well as the determination of the relative binding efficiency of the sample from an average of the remaining data points. Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 17-32; "Further, the user, at step 614, may analyze a specific synthesis region within the grid. If instructed, the system will display the corresponding substrate position, number of photons, number of pixels and the molecular sequence at that synthesis site. The data analysis software also provides the user with many functions which are common to image processing, such as magnification and image enhancement." p. 28, lines 1-7; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.
and a computer for executing the computer program.	"A computer controls the movement of the x-y translation table and data collection. Such devices are discussed in, for example, U.S. Pat No. 5,143,854 (Pirrung *et al.*) incorporated herein by reference for all purposes. See also PCT WO 92/10092 also incorporated herein by reference for all purposes." p. 1, lines 23-29; "Further, translation of the x-y-z table, temperature control and data collection are recorded and managed by an appropriately programmed digital computer." p. 3, lines 5-8; "Photodiode may be, for example, a 13 DSI007 made by

	Melles Griot or equivalent, or other light detection devices, such as photomultiplier tube or avalanche photodiode may be used. Output from the detection device is used by computer 190 to focus the laser at a point on surface 231 of substrate 230." p. 10, lines 26-31; "The output of the C3866 preamplifier/discriminator, via external circuit board 200, is connected to the clock inputs of counters 1 and 2. When counter 1 or counter 2 is gated on, it counts pulses generated by the preamplifier/discriminator; when it is gated off, it ceases to count and computer 190 reads the accumulated number of counts therein. After the computer reads the count from either counter 1 or 2, the counter is re-initialized on the first clock pulse after its gate input goes high. The initialization pulse is about a 50 ns pulse that is generated by the logic in the external circuit board 200 about 50 ns after each transition of the square wave signal from counter 0. The data stored in counter 1 or 2 represents the photon count as a function of substrate position." p. 12, lines 7-20; "The computer reads and stores the voltage generated by the photodiode at step 308." p. 19, lines 19-21; "On the second pass of the loop beginning at step 405, the inverted falling edge (rising edge) of the square wave initializes and enables counter 1 to collect data at steps 406 and 407 respectively. At step 408, the inverted rising edge (falling edge) of the square wave disables counter 1 and data therein is read at step 409 and written to the computer at step 410." p. 22, lines 7-13; "From the information entered by the user and the image file, the system creates a computer representation of a histogram or each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 28-32; "Upon completion of the conversion process, an image file representing fluorescence intensity is created and stored in memory at step 507." p. 25, lines 29-31.

Claim 30 (recited in proposed Count)	**Specification of 08/195,889**
30. A method for evaluating an orientation of a molecular array having features arranged in a pattern, the method comprising:	"Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 22-32; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.
(a) receiving an image of the molecular array produced by scanning the molecular array to determine data signals emanating from discrete positions on a surface of the molecular array;	"Upon completion of the conversion process, an image file representing fluorescence intensity is created and stored in memory at step 507. At step 508, the system may optionally display the image file. The intensity level of the displayed image varies from region to region according to the binding affinity of the targets to the polymer sequence therein. The brightest signals typically represent the greatest binding affinity while signals of lesser intensity represent lesser degrees of binding affinity." p. 25, lines 29-37 "Fig. 6 illustrates one embodiment of the of a system which provides for the removal of these undesirable spurious data points as well as the determination of the relative binding efficiency of the sample from an average of the remaining data points. Referring to Fig. 6, the system is initialized by requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the

	number of pixels versus intensity. At step 606, the main data analysis loop is performed for each synthesis site. Analyzing the histogram for the respective synthesis site, the system calculates the total intensity level and number of pixels for the bandwidth centered around varying intensity levels. For example, as shown in the plots to the right of step 606, the system calculates the number of pixels in the bandwidth using boxcar averaging technique. This process is then repeated until the entire range of intensities have been scanned. At step 607, the system determines which band has the highest total number of pixels. The data form this band is used to derive statistical data for each synthesis site. The statistical data include the peak value, mean intensity and standard deviation of intensity level. Thus, data that are beyond this band are excluded from the statistical analysis. Assuming the bandwidth is selected to be reasonably small, this procedure will have the effect of eliminating spurious data located at both the higher and lower intensity levels. This loop is repeated until all the cells have been processed." p. 26, line 22-p. 27, line 13; Figs. 1A-C show scanners. Figs 2, 3A, 3B, 4A, 4B, 4C and 5 show the system for generating, receiving and analyzing data from an array.
(b) calculating an actual result of a function on pixels of the image lying in a second pattern;	"At step 610, an image in the form of a grid representing the substrate is displayed. Each block in the grid represents a region synthesized with a polymer sequence. The image intensity of each region will vary according to the binding affinity between the polymer sequence and targets therein. Statistical data, such as the peak and average intensity corresponding to each region are also displayed." p. 27, lines 14-20.
(c) comparing the result of step (b) with an expected result which would be obtained if the second pattern had a predetermined orientation on the array; and	"At step 612, the system retrieves the file created during the synthesis process of the substrate being analyzed. The synthesis file contains sequence information as a function of location. The system integrates the synthesis file with the image file and sorts the data therein. Through this process, the molecular sequence of complementary probes and the intensity as a function of location is available." p. 27, lines 31-37.
(d) when the results of the comparison in step (c) are outside a predetermined difference, then altering the orientation of the second pattern on the array and repeating steps (b) and (c), and	"Fig. 6 illustrates one embodiment of the of a system which provides for the removal of these undesirable spurious data points as well as the determination of the relative binding efficiency of the sample from an average of the remaining data points. Referring to Fig. 6, the system is initialized by

repeating the foregoing as needed until the results of the comparison are within the predetermined difference.	requesting the user to enter the name of a image file of interest. At step 601, the system retrieves the image file and prompts the user to enter the four corners of the image at step 602. Next, at steps 603 and 604, the system prompts the user for the number of cells located horizontally and vertically on the substrate. From the information entered by the user and the image file, the system creates a computer representation of a histogram for each cell at step 605. The histogram (at least in the form of a computer file) plots the number of pixels versus intensity." p. 26, lines 17-32; "Further, the user, at step 614, may analyze a specific synthesis region within the grid. If instructed, the system will display the corresponding substrate position, number of photons, number of pixels and the molecular sequence at that synthesis site. The data analysis software also provides the user with many functions which are common to image processing, such as magnification and image enhancement." p. 28, lines 1-7; Figs. 6A and 6B specifically show a method in which an image is obtained and formatted into a grid, the intensities of the pixels are obtained, a grid of regions is displayed, the synthesis file is retrieved, applied to the actual image, and an analysis is performed to detect grid roam, with the potential for reformatting the image.

VII. Conclusion

In view of the above, Applicants respectfully request the Examiner to advance this case to the Board of Patent Appeals and Interferences for the declaration of an interference between Applicants' '613 application and the '196 and '820 patents. Applicants respectfully request the Examiner to handle this matter on an expedited basis, taking into account the pending request for interference filed in the '819 application with respect to the '196 and '820 patents.

Respectfully submitted,
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Date: January 7, 2005

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